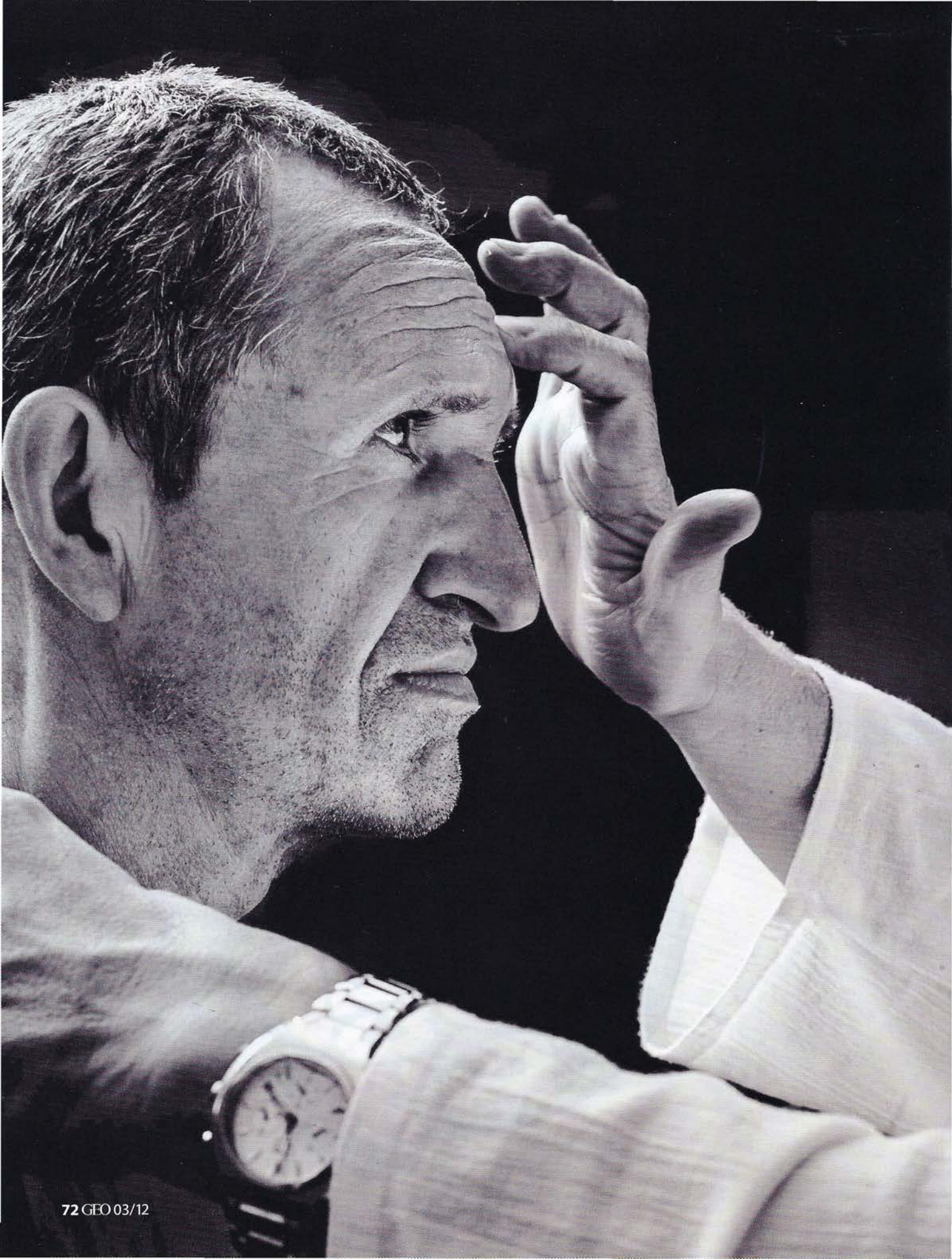
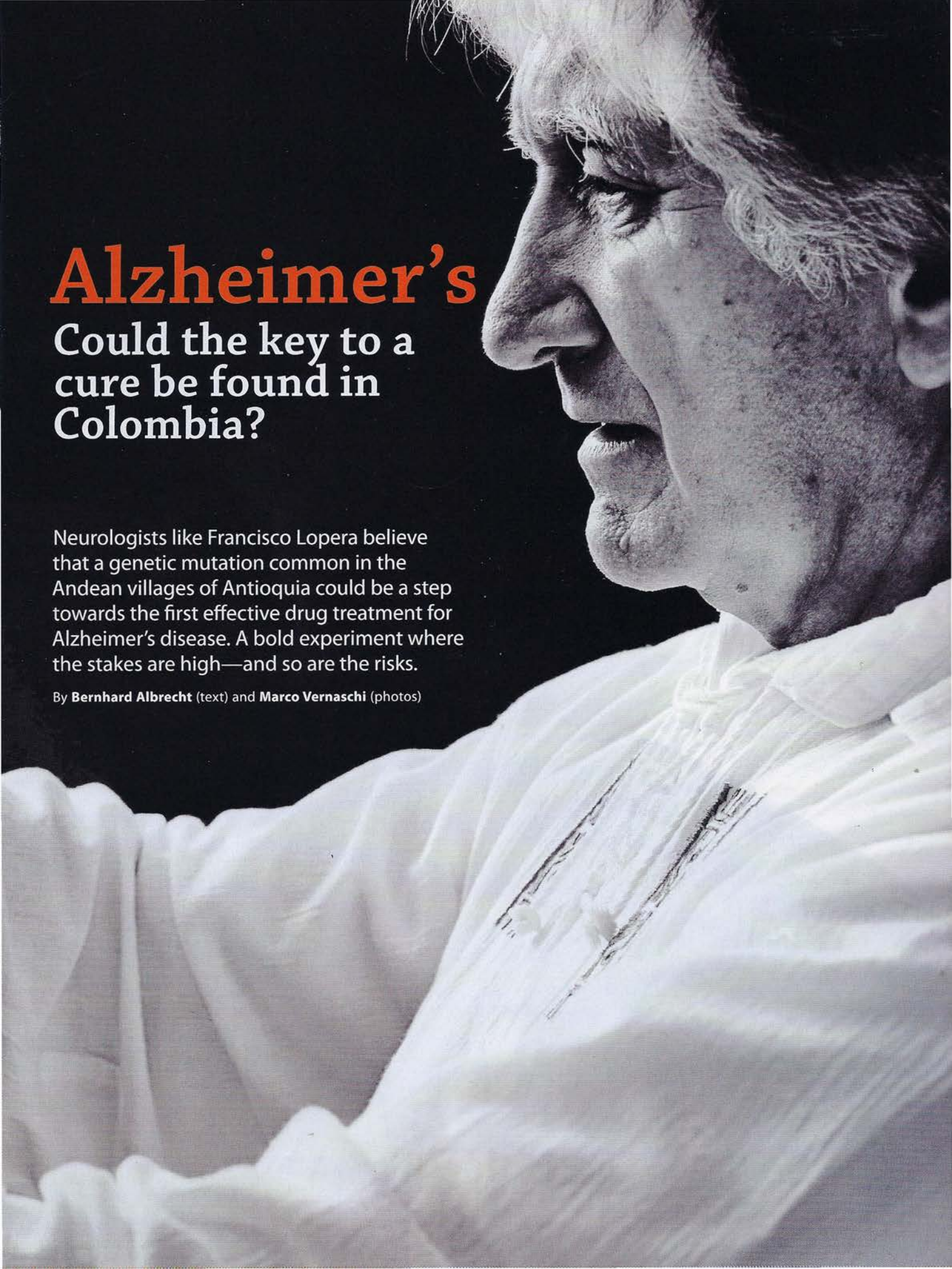


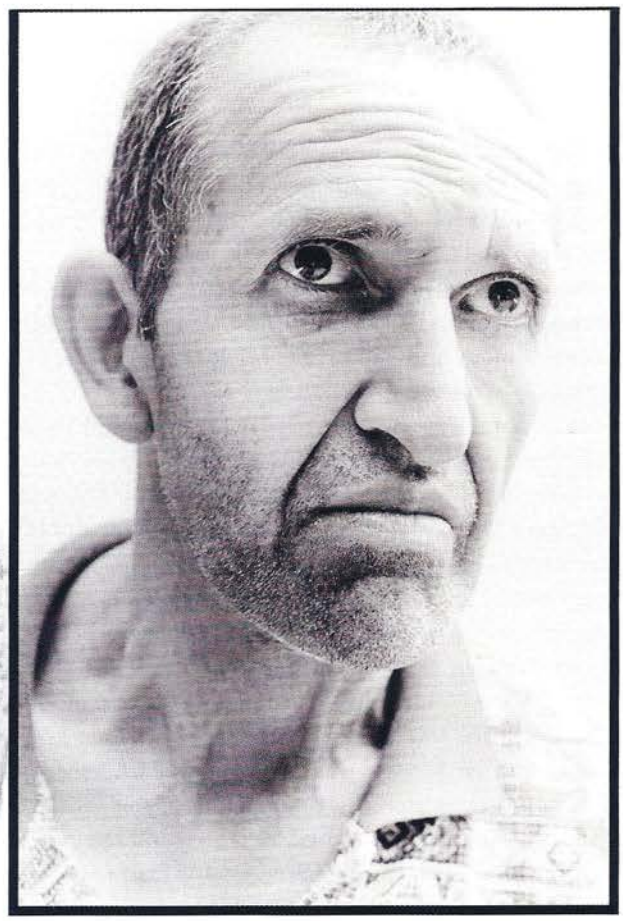


Alzheimer's

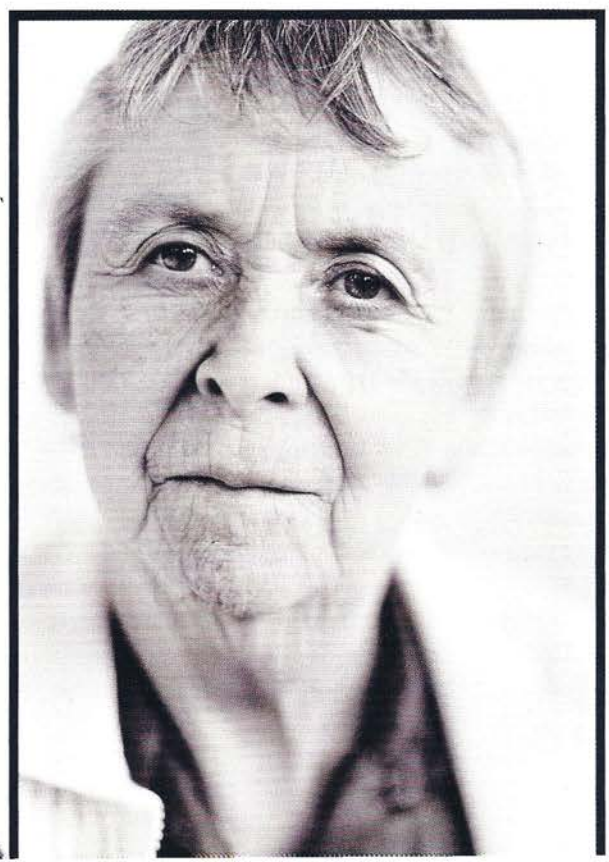
Could the key to a cure be found in Colombia?

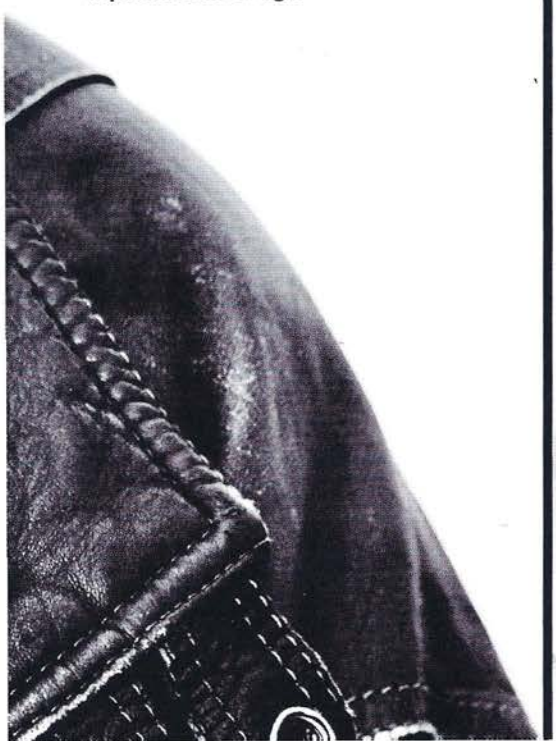
Neurologists like Francisco Lopera believe that a genetic mutation common in the Andean villages of Antioquia could be a step towards the first effective drug treatment for Alzheimer's disease. A bold experiment where the stakes are high—and so are the risks.

By **Bernhard Albrecht** (text) and **Marco Vernaschi** (photos)



The faces of forgetting: these four siblings all suffer from hereditary Alzheimer's which is characterised by an early onset. Large clans of the 'Paisa', a light-skinned community of the Colombian Andes, are stricken by this scourge. It also makes them valuable test-subjects for the latest experimental drugs.





YARUMAL, in the mountains of Antioquia province, is a 5-hour drive from Medellín. The slopes here are steep and the winding road so dangerous that Colombians call it *matasanos*, 'killer of the healthy'.

The seven scientists in the minibus, however, are in high spirits, like boys out on a school trip. They are going to meet the families on whom they will conduct their research in a few months. The scientists hope to interest the farmers of these mountains in a project that neurologist Francisco Lopera has been working on for years: a drug trial that could usher in a new age in pharmaceutical research, an exercise that could someday heal millions, earn billions and mark the beginning of the victory over Alzheimer's.

Everyone in the bus is, therefore, ready with their speech for the farmers. The Paisas, residents of the Andes, know Lopera well. Since the early 1980s, he has been studying the extended family clans in this remote region of Antioquia, clans with thousands of members. The reason that scientists around the world are interested in these people is that a large number of them are stricken at an early age by a hereditary form of dementia.

The pharmaceutical industry and Alzheimer's researchers across the globe have now realised the incredible value of Lopera's discovery: that the rare, genetic type of 'hereditary' Alzheimer's is much easier to investigate than the more common, but also more complicated, 'sporadic' form that affects more than 25 million people, most of them in developed countries.

Lopera is well aware that the project could raise ethical issues. The Paisas will be treated with experimental drugs long before the actual onset of the disease—because studies have clearly shown that damage in the brain starts early and goes unnoticed.

The participants from Antioquia will, therefore, still be young when the trial starts. Many may still want to have children and they are all likely to have years ahead of them free of the genetic malfunction that they may later develop. These are the people who will now be asked to undergo trials with unpredictable risks, as medical trials with Alzheimer's drugs can have unpleasant side effects.

Many a test programme in the United States and in Europe has had to be discontinued because participants developed meningitis, their susceptibility to certain kinds of cancer increased, and there were also deaths.

Most of the Paisas are not well educated. They work in the fields as cowherds or in textile factories. Will they understand the kind of risks they are undertaking?

The men in the bus will have their answer in a few hours.

ANDRÉS QUINTERO* is a potential candidate for the clinical trials. He is only 19, but has already taken one crucial decision: he will not marry or have children—because there is a 50 per cent chance that he could pass on the genetically predisposed Alzheimer's to his progeny—exactly the same chance that he himself stands of having inherited the disease from his mother.

He was just 13 years old, and his mother 43, when she began to repeat questions and become forgetful. Andrés had to help her more and more, and had to take her to work because she would get lost on the way—until she was sacked.

Eventually, one day in August 2007, Andrés Quintero sat in Dr Lopera's clinic and watched his mother try to touch her nose with her index finger—a task she managed only with great difficulty. After 20 minutes, it was proven beyond doubt that her problem was indeed Alzheimer's. And that the disease had also been responsible for the early death of his grandfather. Andrés' sister Adriana may also have inherited the gene. It was then that Andrés decided to be part of Lopera's research.

In those days, Andrés lived with his sister, his mother and his aunt in the town where Adriana was working as an accountant and he himself was studying civil engineering. Andrés remembers watching his mother lose her soul bit by bit every day. "I will never bring a child into this world and expect it to go through what I had to," he declares. But his 26-year-old sister dreams of a family. "I must get started by the time I'm 30. Who knows how long I'll have before Alzheimer's strikes?"

Ever since the siblings learnt of Lopera's drug study, they have hope. "If selected, we will certainly take part, no matter how risky. Anything is better than this disease," says Andrés.

Mari Carmen Zuluaga is free of the disease—so far, at least.

PERHAPS FATE WILL BE KIND to Mari Carmen Zuluaga. At 54, her eyes are still bright and her memory as good as it was 20 years ago. It would be disastrous if she were to now go *bobo*, as the dementia-sufferers are known here, for Mari Carmen looks after her family. She takes care of all those who are no

longer capable of doing so for themselves.

She saw her father die of *la bobera*—'the foolishness'—and all seven uncles and aunts on her father's side. Five sisters and three brothers have also been stricken by the disease, four of whom are still alive. Mari Carmen looks after her brother Felipe, who can't speak any more. Every morning, she helps him from the bed to the shower and gives him a bath. Felipe Zuluaga spends the day on a plastic chair in the living room, as if he himself were a piece of furniture, staring at his hands and rubbing them together constantly.

"He was a wonderful brother," says Mari Carmen, laying a comforting arm around him. "He was always ready to help us out with money whenever we needed it."

Felipe's wandering eyes meet hers. "Do we know each other?" they seem to ask.

"Mama," says Jorge, 34, one of her four sons, "he was also a criminal". And he lists his uncle's offences: car thefts, robberies and at least three murders, resulting in 8 years in prison.

"But today Felipe is the most peaceful man in the world."

Mari Carmen is not scared of the disease. In Angostura, where she grew up, *la bobera* was regarded as much a part of life as death itself. When, at 50, her father began to wear mismatched shoes and beat his wife more and more frequently for nothing at all, the people only said: look, it's got hold of Zuluaga now.

In the past, Mari Carmen believed that the disease was transmitted by a monkey bite. Other people spoke of the curse of a wronged priest or the touch of a mysterious tree. Till the doctor from Medellín told them about a hereditary disease by the name of Alzheimer's.

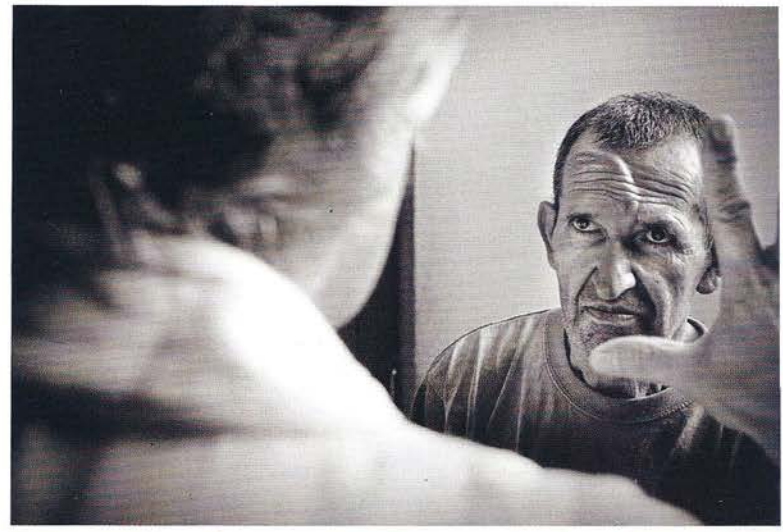
"**MARI CARMEN ZULUAGA. Family C2!**" says Francisco Lopera, unfolding a family tree drawn across two wooden boards as researchers gather around him. "One thousand, five hundred members," he continues. "This is one of the clans we have selected for the first phase of our study; we will meet a few of them in Yarumal." Lopera's pen moves to the top: "These are Mari Carmen's ancestors, traceable back to 1790. Here is the marriage of Javier and Maria. Maria was carrying the gene."

He smiles and his voice rings with pride at having discovered these families. He was a third-year assistant doctor when it all began; now he is 60, an eminent person in his field. It all started in 1982 when a woman brought a 40-year-old farmer to the city and asked the doctor to treat the man's persecution complex. Lopera was amazed that the woman did not appear to find the patient's bed-wetting, his inability to speak or maintain eye contact worth talking about. He then learnt that many others in the farmer's family had lost their memory early on. And so he began to investigate.

Soon, he was spending every free weekend in the mountains. He took blood samples from the farmers and made them

Felipe ZULUAGA

Family C2 has 1,500 members—and one deadly gene mutation.



undergo brain scans. He traced family histories through old church records. Eventually, he came upon more and more affected families.

Lopera's genealogical efforts have revealed 25 families with 5,000 members—the biggest group in the world—with the inherited 'familial' form of Alzheimer's, many of whom start to show symptoms in their early 30s. The 'sporadic' form of the disease, on the other hand, almost never begins before the age of 65. Lopera believed that medical science had much to learn from such families, where many members were guaranteed to develop the disease within a relatively short period of time, while their brain was still free from the normal deterioration brought on by old age.

End of the line: Felipe Zuluaga used to be a thief and murderer, and has been in and out of jail. With the onset of the disease, however, he turned totally docile. Dr Lopera holds up his fingers and tries, in vain, to make him say the number 'three'.

ANDRÉS QUINTEROS' MOTHER has been in a nearby nursing home for a month now. Andrés and Adriana spend every afternoon by her side where she sits slumped in a wheelchair. Andrés kisses her forehead, rubs his cheek on hers, then clasps her forearm and moves it gently up and down. An hour's physiotherapy every day prevents cramps, he knows. When she tenses up, he scolds her gently. He believes she can feel his love, even though she no longer knows who it is that loves her.

In the bed next to her lies her brother Edwin, a taxi driver. In the early days of the disease, he would roam the streets of Medellín, quite lost. The other eight uncles and aunts are as yet unaffected. But they dread every visit to the doctor, for their next memory test could reveal the beginnings of the disease.

LOPERA'S OLDEST COLLEAGUE Ken Kosik is neuroscientist, and former hippie and activist. Without him, the scientists from the University of California would not be sitting in the minibus to Yarumal right now: without him there would *be* no research project.

It was Kosik who brought the Banner Alzheimer's Institute on board—and with it the two renowned psychiatrists, Eric Reiman and Pierre Tariot, who have committed to raise the 50 million US dollars required for the project. Ten million dollars are already in hand from, among others, pharmaceutical companies that are developing Alzheimer's drugs.

For years, Kosik too had tried to sell the project to the pharma industry: "Lots of people would get interested at first, but then back off fearing the incalculable risks," he says.

Kosik travelled to the villages with Lopera for the first time in 1995. During that visit, they made a request to examine the brain of a woman who had just died to confirm their belief that she had Alzheimer's. As long as a patient is alive, Alzheimer's cannot be confirmed: there is always the risk of confusing it with other forms of dementia. Confirmation is possible only through a post-mortem of the brain. Lopera was medical adviser to many patients, the confidant of several families, but had never been able to convince any of them to allow him to perform an autopsy.

Kosik and Lopera prayed with the family at the funeral in

Angostura. Her body was laid out surrounded by her 11 children, her relatives and the *lloranas*—women hired to come and wail.

"All the children agreed to our request," recalls Kosik, "except one son, who was rumoured to be a drug dealer. He accused Lopera of wanting to sell the brain to the *gringos*." The situation threatened to get out of hand; the mayor had to be called to calm the man down. Ultimately, the scientists were allowed to remove the brain in a local hospital. Under the microscope, they were finally able to see the tell-tale signs, exactly as described by Alois Alzheimer back in 1907.

There were abnormal deposits between the nerve cells of the dead woman; hard, insoluble amyloid plaques, formed by the accumulation of protein fragments called beta-amyloids. These plaques are like garbage dumps in the brain, each spread over an area about a tenth of the size of the dot on this 'i'. And inside the nerve cells they found thick bundles of tau proteins called neurofibrillary tangles.

Under normal circumstances, tau proteins stabilise the transport of materials between nerve cells. In Alzheimer's disease, however, these tau proteins are altered and the transport networks collapse. There was no doubting the evidence: the woman from Angostura had suffered from Alzheimer's.

Around this time, the international research community began to show an interest in groups with genetically predisposed Alzheimer's disease. More than 500 such families are known worldwide. In all of them, hereditary gene mutations lead to changes that are also typical of the more common sporadic form of Alzheimer's. Scientists now wanted to understand what function the mutated genes normally have in order to pinpoint the causes that lead to Alzheimer's dementia.

Kosik and Lopera looked feverishly for the mutation that causes mental derangement in the Paisa. They suspected chromosome 14—because, in all the affected Paisas, one solitary alphabet of the genetic code located on this chromosome was different from that of a healthy person.

Four months before Kosik and Lopera found the answer, US scientists studying another Alzheimer's family discovered the PS-1 gene in precisely the same location. Today, 185 different mutations are known in this one gene alone, all of which trigger Alzheimer's. The age of onset depends on the position where the change occurs: members of the American family were affected at an average age of just 27. All inherited mutations known so far impact genes that influence the production of the beta-amyloid protein—the same protein that accumulates in the brain of Alzheimer's patients in the form of plaques.

Was this the breakthrough? Could drugs be developed to target the pathologically altered protein and render it harmless?

To test such drugs, however, one would have to start with the experimental therapy long before dementia actually sets in, because often the protein begins to accumulate even a decade before the memory loss manifests. And the largest Alzheimer's

Andrés QUINTERO

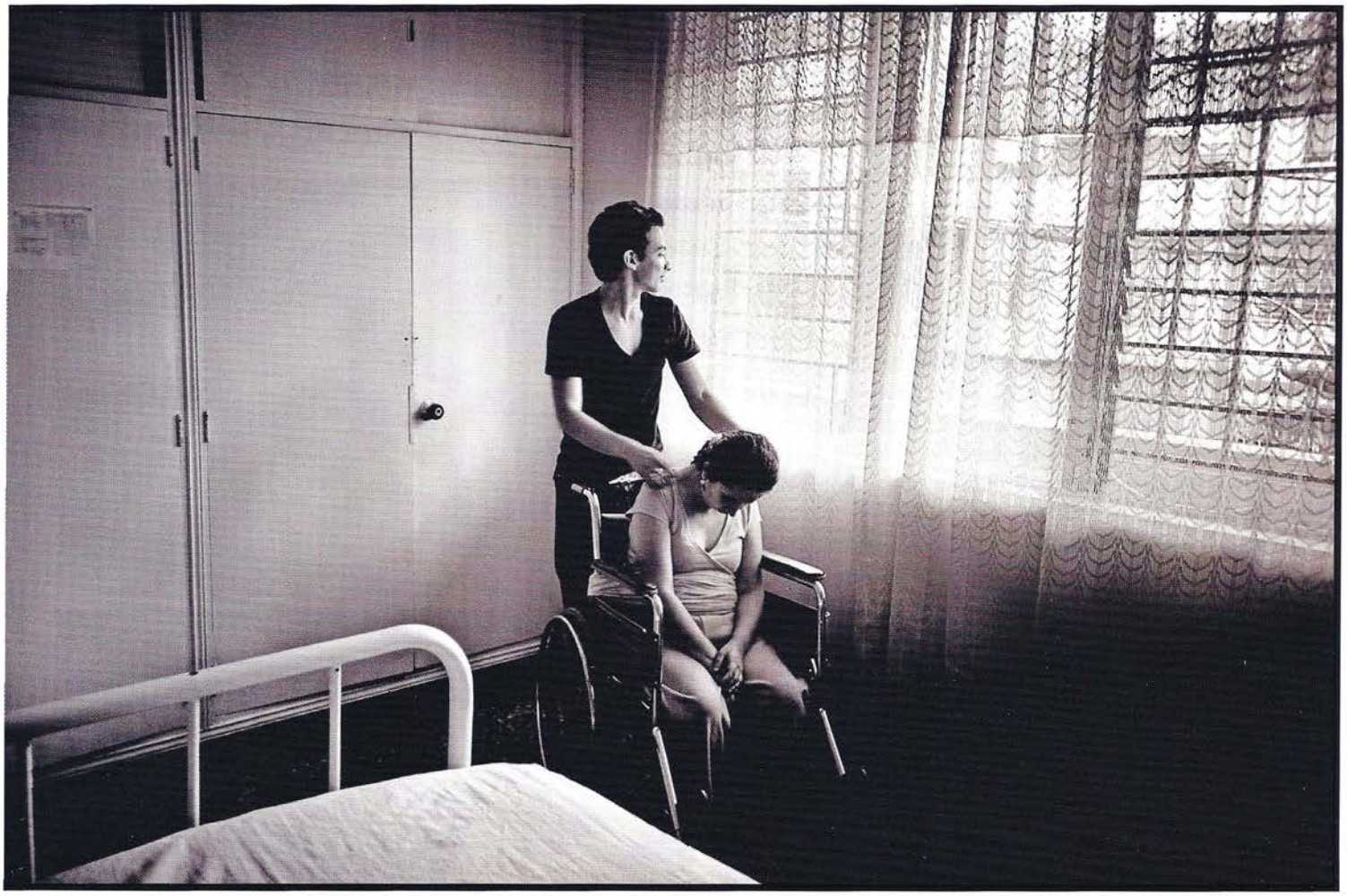
He stands a 50/50 chance of developing the disease that afflicts his mother.

group in the world, that very one in Colombia, was ideal for such trials; it was exactly the group that scientists had been seeking.

WHEN ERIC REIMAN and Pierre Tariot, the two psychiatrists from the Banner Alzheimer's Institute, describe their research project in Colombia, it reads almost like a declaration of war. There is talk of a 'call to arms,' of overcoming the 'roadblocks' that stand in their way. Reiman and Tariot want the US Food and Drug Administration to allow promising drugs to be released to the market far earlier than is permissible today.

According to current rules, a substance must first clearly prove that it prevents or heals a disease. "That will just take too long," says Reiman. He would like to treat Alzheimer's preemptively, at least 10 years before the first symptoms appear. By the time they had conclusive proof that the drug does indeed prevent the onset of dementia, the patent would have long expired, which wouldn't be much use to the pharmaceutical industry.

The Banner Alzheimer's Institute wants to take a different



Andrés Quintero was still a child when his mother developed dementia. At an age when his friends are out partying, he feeds and bathes his mother, puts her to bed and reads to her. After 3 years, he has had to admit her to a nursing home.

path. In future, certain biomarkers—early biological indicators—will play a critical role in the administration of an Alzheimer's drug. With the Paisa study, the scientists want to prove that this can work. Lopera's team has, in fact, identified such biomarkers that show up many years before memory loss begins. For instance, there is a premature decline in the level of Alzheimer's proteins in the spinal fluid—a sign that they are accumulating in the brain and destroying nerve cells there.

Lopera has selected 1,500 Paisas for the first phase of the study. Their names will be coded as numbers and tests will determine who among them carry the gene mutation. Of course, neither doctors nor patients will know the results of the gene tests—which is normal in such experiments. Only a biostatistician will have access to the confidential list of names.

The selected Paisas will begin with the experimental therapy at an average age of 35, a good 10 years before the usual onset of the disease in this population. For 2 years, the scientists will treat one group with a particular drug and will monitor how the relevant biomarkers change. The other participants of the study will receive a placebo.

If the medication effects an improvement, the treatment will continue for "a little bit longer," in the words of Tariot. If not, the next "most promising drug" will be tried. At the same time, researchers will test the same drugs on healthy older people in the United States. The subjects chosen there belong to a population group that is not guaranteed, like the affected Paisas, to develop Alzheimer's, but is, nevertheless, very likely to develop the disease in their old age.

Should a drug succeed in preventing or even delaying the onset of Alzheimer's dementia in both the test groups, this would open up a multi-billion-dollar business opportunity. Theoretically, anyone above 65, who can afford it, would be eligible for the preventive treatment. And a drug that delays the onset of the disease by even 5 years could halve the number of potential Alzheimer's patients in the world.

THE RESEARCHERS' VISION OF the future is based on the theory that both the familial genetically predisposed

Alzheimer's and the sporadic version are triggered by a single root cause, one that can be combated with the same drug. Most drug companies are relying on that.

The only thing is, there's no proof—yet.

Lopera believes that the chances of success are comparatively high for the Paisa patients in Colombia. The drugs have already been tested on mice. Alzheimer's in mice is also derived from a mutation—in the same gene that gets altered in the Paisas. Lopera would like to use only those drugs that have proven to be quite safe in the case of several hundred patients already suffering from Alzheimer's.

And even then, only a fifth of the more than 50 drugs that are presently being developed around the world are being considered. It is as yet unclear on which particular drug the choice will ultimately fall. "Everything can change so quickly," says Ken Kosik. "One pharmaceutical company may lead the way today, but it may have to discontinue its study tomorrow." Like the firm Eli Lilly that had to halt its trials in 2010 with 2,600 Alzheimer's patients from 31 countries. To the researchers' surprise, the dementia spread faster in those who had received the drug than in those treated with a placebo; furthermore, the risk of a particular kind of skin cancer rose sharply.

For Lopera and his team, using this drug would be absolutely out of the question.

ARRIVAL IN YARUMAL is a homecoming for Lopera. He grew up in Yarumal, his siblings still live here, and people are proud of the famous son of the city. He and his colleagues in the minibus now halt at a small hospital.

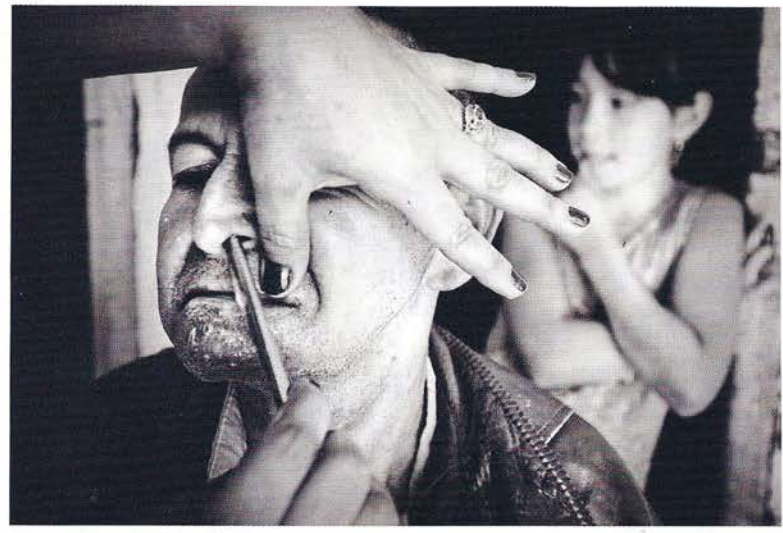
Every chair in the main auditorium is occupied and members of the Alzheimer's families crowd at the back, several rows deep. Among the audience are many young faces: men with gelled hair and jeans, girls in short skirts, and children. Everyone rises for the national anthem. The son of the city stands at the podium, his hand on his heart.

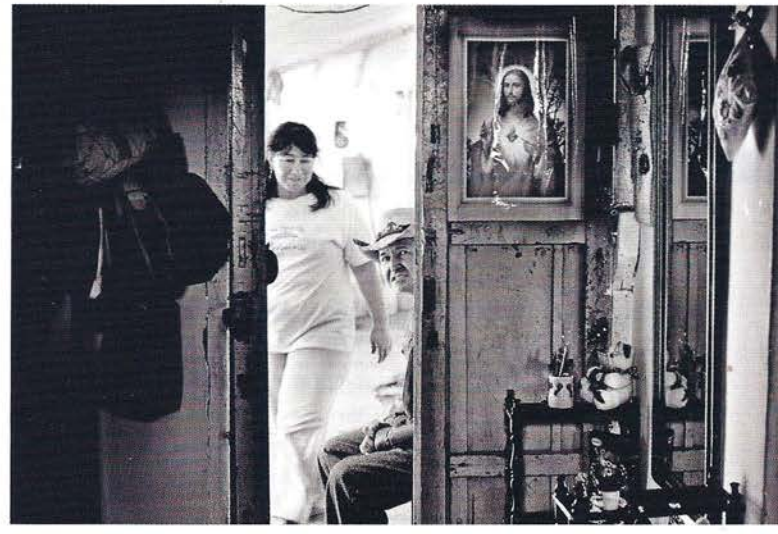
Then he launches into his lecture: 20 minutes of top-speed talking, peppered with technical terms. The audience's attention drifts, but one sentence stands out: "Many of you have become impatient with us over the last few years because we have only asked you questions and never been able to help. All that is about to change."

Then Lopera's colleague Eric Reiman takes the mic. He speaks slowly, as someone translates into Spanish. Reiman speaks of the "privilege" of getting to know the families here, of understanding "the adversity in which all of you find yourselves" and of "our hope" that drugs will be more effective if they are administered years before the onset of the disease. Reiman also speaks of the risks, but very generally. He does not mention how grave they were in the earlier trials, that people had died. He agrees with Lopera: it is too early for such discussions. Any questions?

Alejandro ZULUAGA

By the time the first symptoms show up, it is already too late for treatment.





"What should I ask for at the chemist's, if I want such a drug now?"

"Can I catch the illness from my father while I am taking care of him?"

"What about drug abuse? I am told that causes Alzheimer's."

An hour and a half later, there is thunderous applause for the researchers. Clusters of people gather around the podium as the Paisas storm them with further questions.

"We must ensure that everyone understands participation is voluntary and that they can change their mind at any stage," says Reiman later. "And also what it means when we talk of risks."

Hope versus risks—this is the dilemma the Paisas will have to face. Jorge and his brother have already decided. If Lopera

Coffee farmer Alejandro Zuluaga used to be a placid man. At 43, he turned violent, once almost strangling his daughter Inma. Dramatic personality changes appear in the Paisa much earlier than in people who are affected by the sporadic form of the disease

offers them the treatment against Alzheimer's, they will take the drugs. "I was always a fighter," says Jorge and laughs. Four days after the talk, the Zuluaga family comes to Medellín: to give blood samples, and undergo a medical examination and a new brain scan. This will help in differentiating, at an early stage, the symptoms of Alzheimer's disease from any other brain disorder.

"My god," whispers Jorge, "this is tough." The monitor shows three shapes for two seconds: yellow cross, green triangle and blue rhombus. Which shapes has he seen, which colours? Carriers of the mutated gene have difficulty with this test even before the onset of the disease. Jorge struggles, too: "Red cross, blue triangle, green semicircle?"

No need to worry, an assistant reassures him. With just 3 years of formal schooling, this is only to be expected. A little later, his smile is back and he agrees with his brothers that the tests had been great fun. Now they just have to hope that they are not placed in the group that will receive the placebos. **IN THE EVENING,** Andrés Quintero sits at the computer and reads up the latest reports on Alzheimer's. He knows most of the headlines by heart: New Alzheimer's Gene Found, Protein Promotes Alzheimer's, Pharma Company Starts New Study on Mice. He still cannot shake a chance remark by a Spanish neurologist that he read 2 years ago: "There will never be a drug for Alzheimer's."

Despite all this, Andrés has not given up hope. But perhaps it is just as well that his family has not been selected for the initial trials with the new drugs, he says: "I am still young. The later I begin with them, the better. Who knows what the side effects might be?" But if Alzheimer's were to be treatable one day, he adds, then he too would like children of his own. ■

■ ■ ■ MARCO VERNASCHI *and* BERNHARD ALBRECHT *saw first-hand in Colombia how well people deal with Alzheimer's when there is family support. Vernaschi's previous assignments included subjects like the illegal organ trade. Albrecht is a science journalist based in Munich, who writes largely on medical ethics.*